

BASIC RESEARCH

Non-invasive evaluation of atherosclerosis with contrast enhanced 16 slice spiral computed tomography: results of ex vivo investigations

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Objective: To evaluate the diagnostic accuracy of 16 slice computed tomography (CT) in determining plaque morphology and composition in an experimental setting. The results were compared with histopathological analysis as the reference standard.

Methods: Nine human popliteal arteries derived from amputations because of atherosclerotic disease were investigated with multislice spiral CT (MSCT). Atherosclerotic lesions were morphologically classified (completely or partially occlusive, concentric, eccentric), and tissue densities were determined within these plaques. In addition, vessel dimensions were quantitatively measured.

Results: The results were compared with histological analysis. The concordance index κ for morphological classification was 0.88. Plaque density ($n = 51$ lesions) was significantly different ($p < 0.0001$) between lipid rich, fibrotic, and calcified lesions (Stary stage III: $n = 2$, 58 (8) Hounsfield units (HU); Stary V: $n = 11$, 50 (21) HU; Stary VI: $n = 14$, 96 (42) HU; Stary VII: $n = 6$, 858 (263) HU; Stary VIII: $n = 18$, 126 (99) HU). The concordance index κ for the classification of plaques based on density was 0.51. Vessel dimensions had a good correlation ($r = 0.98$).

Conclusions: 16 slice CT was found to be a reliable non-invasive imaging technique for assessing atherosclerotic plaque morphology and composition. Although calcified lesions can be differentiated from non-calcified lesions, the diagnostic accuracy in further subclassifying non-calcified plaques as lipid rich and fibrotic is low, even under experimental conditions.

Cardiovascular disease is still the main cause of death in the industrialised world. Many patients with an acute coronary syndrome do not have a history of symptoms of atherosclerotic disease. According to a recently published review these patients are referred to as vulnerable patients.^{1, 2} Diagnostic strategies that assessed patient history, several cardiovascular risk factors, and biomarkers were found to be useful in detecting these patients.

Because of rapid technical developments with significantly improved image quality, new non-invasive imaging modalities, such as multislice spiral computed tomography (MSCT),^{3–5} magnetic resonance imaging,^{6, 7} and electron beam computed tomography (EBCT)^{8, 9} have a potential role in the characterisation of vulnerable patients. Coronary calcifications, which can be detected by MSCT and EBCT, are indicative of the presence of coronary artery disease.^{9–11} However, the absence of calcifications does not exclude coronary artery disease.^{12, 13} Owing to improved temporal and spatial resolution MSCT provides non-invasive visualisation of human coronary arteries and atherosclerotic lesions.^{1, 2, 6, 14, 15} Initial studies indicated that non-calcified atherosclerotic plaques may be detected by contrast enhanced four slice computed tomography (CT).^{16, 17}

The purpose of the present study was to evaluate the diagnostic accuracy of 16 slice CT in determining plaque morphology and composition in an experimental setting. The results were compared with histopathological analysis as the reference standard.

METHODS

Nine human popliteal arteries were scanned by 16 slice CT after amputation of the lower limb because of atherosclerotic

disease (vessel length 8–14 cm). The study protocol was approved by the local ethics committee.

Experimental prestudy

An experimental prestudy was performed to evaluate the contrast attenuation of various contrast medium–saline dilutions aimed at detecting the correct dilution to achieve a contrast enhancement comparable with those achieved in clinical studies of about 200–250 Hounsfield units (HU).¹⁸ Silicon tubes (diameter 6 mm, wall thickness 1 mm, lumen diameter 4 mm, wall density 188 HU) were used to simulate arteries.¹⁹ These tubes were filled with various contrast medium–saline concentrations ranging from 1:20–1:110. The tubes were scanned by spiral scan technique with 120 kV, 500 mA, rotation time 0.42 seconds, collimated slice width 16×0.75 mm, and spiral pitch 2.8. The raw data were reconstructed with an image increment of 0.5 mm, a slice width of 1 mm, and a medium sharp convolution kernel (B30f). Density was measured five times within the contrast enhanced lumen.

Pathological examination

The popliteal arteries were isolated, prepared, and transported on the day of amputation to the Department of Radiology to be examined by MSCT. The entire vessel was filled under pressure with a contrast medium–saline mixture to achieve accurate filling of the arteries and to prohibit collapsing. After completion of MSCT, the arteries were immediately fixed under pressure, embedded in paraffin,

Abbreviations: CT, computed tomography; EBCT, electron beam computed tomography; HU, Hounsfield units; MSCT, multislice spiral computed tomography; PROCAM, prospective cardiovascular Munster

histologically sectioned in 5 mm slices, and stained with haematoxylin and eosin. An experienced observer who was blinded to the MSCT results quantitatively measured vessel diameter and qualitatively analysed plaque morphology and composition. The results were set as the reference standard. All analyses were performed with a Leica DMLB (Leica, Wetzlar, Germany) microscope. Plaque morphology was classified as follows: completely occlusive, partially occlusive, concentric, and eccentric. Plaques were defined as partially occlusive if they were not circular (defined as concentric) or sickle shaped (defined as eccentric) but had a luminal narrowing. Plaque composition was classified according to the updated eight stage Stary classification.²⁰

Computed tomography

The popliteal arteries were embedded in a bowl filled with ultrasound gel to avoid direct contact with air. A mechanical 16 slice CT machine (Sensation 16, Siemens Medical Solutions, Forchheim, Germany) was used for all investigations. This technology allows for the application of dedicated spiral algorithms that provide a temporal resolution down to 185 ms and a spatial resolution of up to 11 line pairs/cm ($0.5 \times 0.5 \times 0.75$ mm).⁵ The proximal end of the popliteal artery was cannulated with a 5 French balloon catheter (6.0×2.0 mm) to seal the proximal vessel segments and to allow the artery to be completely filled with contrast medium. A concentration of contrast medium to saline of 1:80 (Imeron 400; Altana, Konstanz, Germany) was used to achieve optimal contrast attenuation of the popliteal artery (fig 1). The contrast medium was injected continuously at $1.5 \text{ cm}^3/\text{s}$ with an injection pump. The scan protocol was adapted to the protocol used for in vivo scanning of the coronary arteries.^{3,4} The scan protocol was as follows: 120 kV, 500 mA, rotation time 0.42 seconds, collimated slice width 16×0.75 mm, and

spiral pitch 2.8. In each scan 50–100 axial slices were obtained. The raw data were reconstructed with an image increment of 0.5 mm, a slice width of 1 mm, and a medium sharp convolution kernel (B30f). The matrix size was 512×512 and the field of view for image reconstruction was set at 100×100 mm. Data were further analysed on an offline workstation (Leonardo, Siemens Medical Solutions).

To facilitate direct comparison between MSCT and histopathological results, the presence of atherosclerotic plaques was evaluated in 5 mm steps on axial slices (every fifth slice), as well as on maximum intensity projections (650 HU window, 230 HU level). In addition, anatomical orientation points, such as side branches, were used to ascertain exact alignment of MSCT and histological results.

Vessel diameter was quantitatively measured on the selected slices. The morphology of detected plaques was classified as completely occlusive, partially occlusive, concentric, and eccentric. Plaque composition was evaluated by measuring density. Density was measured five times within the predominant tissue of each plaque at five different places with a region of interest ranging from 30–50% relative to the plaque area. The region of interest was adapted to the plaque size. Each plaque was then characterised by mean and median values. All measurements were taken by one independent observer who was blinded to the histological results.

Statistical analyses

Continuous variables are presented as their mean (SD) and median. The results of plaque morphology (completely occlusive, partially occlusive, concentric, and eccentric) determined by MSCT were compared with the reference standard histological analysis by contingency analysis. The concordance index κ was calculated. Density was measured five times within each plaque area. The comparison of plaque density as determined by MSCT with the histological classification was based on the median of the five density measurements. Box and whiskers plots showing range and quartiles were used to describe the results of the density measurements. Analysis of variance was performed to compare the results of the density measurements of the plaque groups. The nominally scaled histopathological parameters—calcified plaque, fibrotic plaque, lipid rich plaque, and thrombus—and the MSCT measurements were compared by logistic regression analysis. The multivariate model estimated the probability that the density values belonged to one of the nominal values. A contingency analysis was performed to evaluate whether the statistically estimated plaque composition corresponded with the histological reference standard. Probability values of $p < 0.05$ were considered significant. All analyses were performed with JMP 4.0 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Figure 2 summarises the results of the dilution experiments. The density of the mixture of contrast agent and saline diluted 1:80 was 237 (17) HU. Since attenuation values of 200–250 HU within the contrast enhanced popliteal arteries were desired, this mixture was used for the ex vivo studies.

Morphological classification

Fifty seven histological sections were evaluated histologically: 16 (28%) were classified by the reference standard as completely occlusive, five (9%) as partially occlusive, 26 (46%) as concentric, and 10 (18%) as eccentric. Because of a technical defect of the MSCT scanner, only 47 of 57 plaque areas could be compared with MSCT: 15 (32%) were classified as completely occlusive, five (11%) as partially occlusive, 18 (38%) as concentric, and nine (19%) as

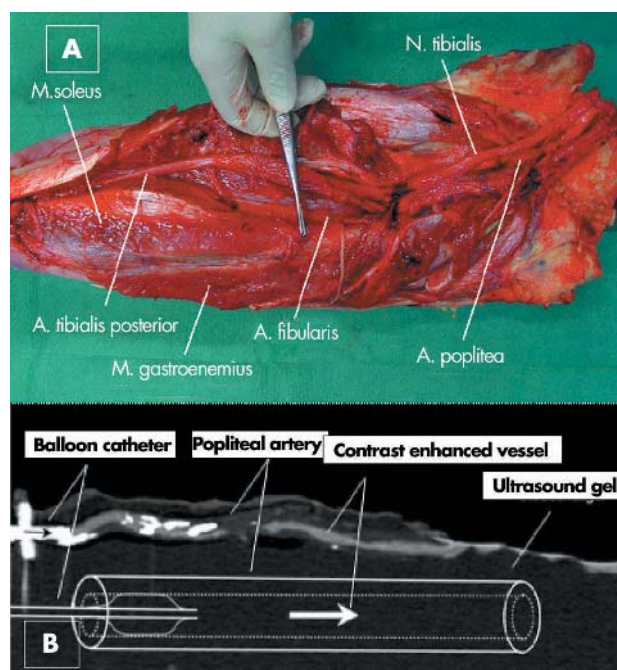


Figure 1 Multislice spiral computed tomography (MSCT) example of a contrast enhanced popliteal artery. (A) Image example of artery preparation for MSCT acquisition. A fibularis, fibular artery; A poplitea, popliteal artery; A tibialis posterior, posterior tibial artery; M gastrocnemius, gastrocnemius muscle; M soleus, soleus muscle; N tibialis, tibial nerve. (B) Contrast enhanced popliteal artery with both calcified and non-calcified plaques.

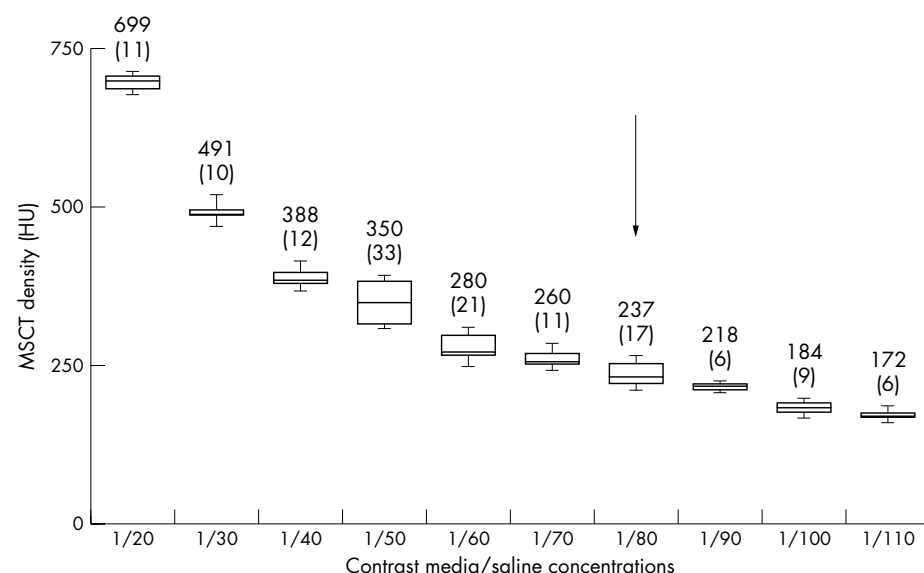


Figure 2 Densities of various contrast medium-saline concentrations in box and whiskers plot showing range and quartiles. The box extends from the 25th centile to the 75th centile, with a line at the median (50th centile). The whiskers extend above and below the box to show the highest and lowest values. The arrow indicates the density of a 1:80 dilution. Mean (SD) densities are given. HU, Hounsfield units.

eccentric. The MSCT investigator classified plaque morphology as follows: all complete occlusions were correctly classified, three of five partial occlusions were correctly detected (two were misclassified as eccentric), 17 concentric plaques were correctly classified (one was misclassified as eccentric), eight eccentric were correctly classified (one was misclassified as concentric). The concordance index κ for the morphological classification was 0.88. Sensitivity, specificity, and positive and negative predictive values of MSCT in classifying plaque morphology were as follows: completely occlusive, 100%, 100%, 100%, and 100%; partially occlusive, 60%, 100%, 100%, and 94%; concentric, 94%, 97%, 94%, and 97%; and eccentric, 89%, 97%, 89%, and 92%, respectively.

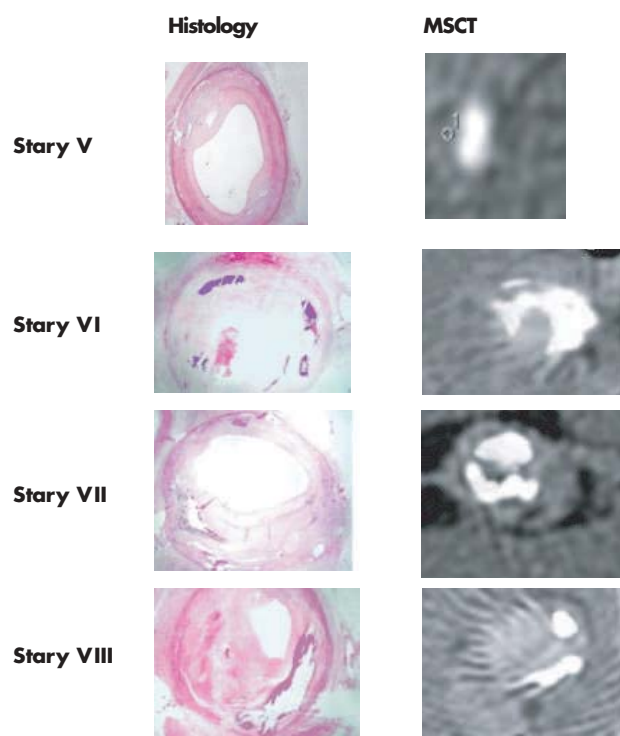


Figure 3 Image examples of Stary stage V–VIII plaques comparing histological with corresponding MSCT slices. Haematoxylin and eosin stain.

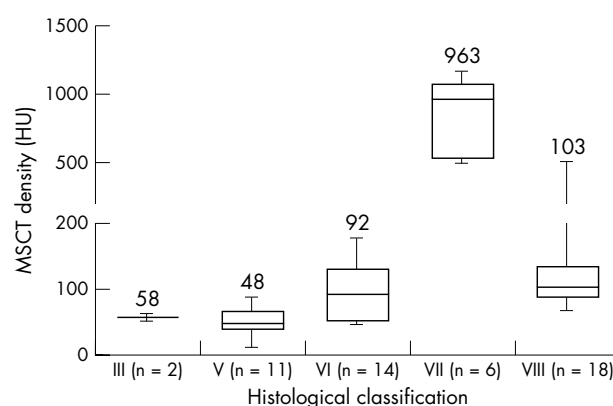


Figure 4 Comparison of histological classification with MSCT density measurements in box and whiskers plot showing range and quartiles. The box extends from the 25th centile to the 75th centile, with a line at the median (50th centile). The whiskers extend above and below the box to show the highest and lowest values. Data are medians.

Quantitative measurements

Quantitative measurements were taken on 84 slices and sites to determine the vessel diameter. The following results were obtained for vessel diameter: 6.44 (1.6) mm by histological analysis versus 6.92 (1.6) mm by MSCT (Pearson $r = 0.97$, $p < 0.0001$). Bland-Altman analysis showed a mean difference between the vessel diameters of 0.49 (0.36) mm (95% confidence interval 0.41 to 0.57).

Determination of plaque density

Plaque composition was histologically evaluated on 51 slices and classified according to Stary²⁰ as follows: two were stage III, 11 were stage V, 14 were stage VI, six were stage VII, and 18 were stage VIII (fig 3). Results of MSCT density measurements within these plaques were as follows: Stary stage III: 58 (8) HU (median 58); stage V: 50 (21) HU (median 48); stage VI: 96 (42) HU (median 92); stage VII: 858 (263) HU (median 963); and stage VIII: 126 (99) HU (median 103). These results were significantly different ($p < 0.0001$) for lipid rich (III/V), fibrotic (VIII), and calcified lesions (VII).

Classification of plaques based on MSCT density values

As fig 4 shows, an overlap in density values between the different plaque groups was obvious. Thus, a multivariate analysis was performed to evaluate the accuracy of classifying plaque composition based on density measurements. Stary III and V plaques were regarded as lipid rich, VI as thrombi, VII as calcified, and VIII as fibrotic.

All six calcified plaques were classified correctly. Fourteen of 18 fibrotic plaques were classified correctly; one was misclassified as calcified, one as lipid rich, and two as thrombi. Thirteen of 14 lipid rich plaques were classified correctly; one was misclassified as fibrotic. Only one of 14 Stary VI plaques was classified correctly (eight were misclassified as fibrotic and five as lipid rich plaques). The overall concordance index κ for the classification of plaques was calculated as 0.51 (without thrombi as nominal parameter, $\kappa = 0.56$). Sensitivity, specificity, and positive and negative predictive values of MSCT in classifying plaques was as follows: lipid rich, 92%, 84%, 67%, and 97%; fibrotic, 78%, 73%, 61%, and 86%; calcified, 100%, 98%, 86%, and 100%; and thrombi, 7%, 95%, 33%, and 73%, respectively.

DISCUSSION

The most important findings of the present study are summarised as follows: (1) contrast enhanced MSCT allows for an accurate determination of the morphology of atherosclerotic plaques; (2) tissue density determined within atherosclerotic lesions corresponds well with plaque composition; and (3) our results indicate that plaques with predominantly lipid rich and fibrous tissue have different MSCT attenuation values. However, correct classification is limited because of overlapping test results.

Non-invasive determination of plaque morphology by MSCT

Various clinical studies focused on the visualisation of intracoronary lesions, indicating a steadily improving diagnostic accuracy of MSCT in detecting clinically relevant stenoses. However, the non-invasive determination of plaque morphology has not been addressed so far. Our results indicate that plaque morphology can be reliably classified by MSCT, at least under experimental conditions with a motionless model. This appears to be of special clinical importance, since both plaque composition and lesion morphology were found to predict plaque stability. Yamagishi *et al*²¹ described in an in vivo study with intracoronary ultrasound as the reference standard that eccentric plaques are more likely than concentric plaques to rupture.

Density measurements and plaque composition

MSCT technology with 16 detector slices allows for non-invasive visualisation of human coronary arteries with diagnostic image quality in vessel segments > 1.5 mm diameter.^{4, 18, 22} Immediately after the introduction of MSCTs it became apparent that not only hyperdense but also hypodense areas within contrast enhanced axial slices could be detected.²³ We recently showed that plaque echogenicity as determined by intracoronary ultrasound corresponds well with plaque density on contrast enhanced four slice CTs.¹⁷ Since partial volume effects, beam hardening, and iodine attenuation may affect the precision of density measurements in clinical studies, a standardised contrast attenuation of about 200–250 HU is required to assure meaningful and comparable results.¹⁹

The results of the present study comparing MSCT plaque density measurements with the histopathological reference standard are in keeping with and confirm the initial clinical

data. Our results indicate that 16 slice CT allows for non-invasive visualisation of the stages of atherosclerosis. A limitation remains that intracoronary thrombi may be misclassified as non-calcified plaques due to similar attenuation values.

Furthermore, as fig 4 indicates, an overlap of density values between lipid rich and fibrotic plaques is obvious. This had an important impact on the diagnostic accuracy, and only 51% of all plaques were classified correctly by MSCT criteria. Thus, further subclassification of non-calcified lesions is limited even in this experimental study.

Quantitative measurements with MSCT

Reliable quantitative measurements within coronary arteries are important for clinical practice—for example, for planning interventions in severe lesions.^{24–26} The presented results are in keeping with initial experimental and clinical reports indicating that quantitative measurement with MSCT is accurate.

MSCT and the vulnerable patient

Recently Naghavi *et al*^{1, 2} discussed the potential value of non-invasive imaging modalities in detecting the vulnerable patient for acute coronary events. The basis of the diagnostic pyramid described was a clinical examination, the patient's history, and the use of established risk scores, such as those used in the Framingham²⁷ and PROCAM (prospective cardiovascular Munster) studies.²⁸ Since these allow for calculation of relative risk only, implying that only a certain percentage of a patient population obviously is at risk, additional diagnostic efforts are required to characterise the vulnerable patient further. We showed in the present study that MSCT allows for non-invasive detection of the stages of atherosclerosis, including calcified and non-calcified lesions. Thus, this technique may theoretically close the gap between relative risk and actual morphological changes in the arteries.

Leber *et al*¹² recently showed that patients with acute coronary syndromes had a significantly higher number of non-calcified coronary plaques than did patients with stable angina pectoris. We recently showed that high risk patients (PROCAM above the third quintile) without detectable coronary calcifications still have non-calcified plaques with a prevalence of 10%.²⁹

Randomised, large scale, prospective studies are needed to determine whether the detection of calcified and non-calcified plaques by MSCT may play a part in the diagnostic algorithm to detect the vulnerable patient.

Limitations of MSCT imaging

A major limitation of MSCT for its use as a screening test is the high radiation exposure of about 5–10 mSv.^{30, 31} However, MSCT technology is being further improved with reduced tube current during systole, nearly halving radiation exposure,³² as well as the development of scanners with additional detector slices allowing for shorter examination times and presumably stabilised image quality.

Also, the need for iodinated contrast media was reduced to about 80 ml for one scan and is now in the range of conventional coronary angiography.³³

Other non-invasive imaging modalities such as magnetic resonance imaging and EBCT require no or less radiation. However, no data on a systematic evaluation of non-calcified plaques by EBCT are available, and the value of routine magnetic resonance imaging of plaque is under clinical investigation.

Study limitations

The current ex vivo study was performed in human popliteal arteries free of motion and breathing artefact to allow for a

direct comparison of MSCT findings with the histopathological reference standard. The purpose of the study was to evaluate the accuracy of MSCT in differentiating plaque morphology and composition. Since plaque areas on selected slices only and not entire plaques were analysed, we have no information on the sensitivity and specificity of detecting atherosclerotic plaques. In addition, the minimum plaque volume required for MSCT detection is unclear. These issues need to be addressed by future studies, ideally with the use of intracoronary ultrasound in in vivo studies. All popliteal arteries were in advanced stages of atherosclerosis, as opposed to the situation in most patients in whom MSCT would be applied—for example, for screening purposes. The sample was too small to establish reliable thresholds for the differentiation of plaque morphology. As indicated by the mean high density values of fibrotic plaques (126 (99) HU) determining the median (103 HU) may also be useful. This has to be evaluated by further studies with larger sample sizes.

However, since our goal was to evaluate the accuracy of differentiating plaque morphology non-invasively by determining density within plaques by MSCT, our principle conclusions are not affected.

Conclusions

Sixteen slice CT was found to be a reliable non-invasive imaging technique for assessing the stages of atherosclerosis. Although calcified lesions can be reliably differentiated from non-calcified lesions, the diagnostic accuracy in further subclassifying non-calcified plaques as lipid rich and fibrotic is low, even under experimental conditions.

The role of MSCT in the diagnostic algorithm of vulnerable patients needs to be addressed by further clinical studies.

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